For Reference

NOT TO BE TAKEN FROM THIS ROOM

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR Ming Kai Wong

TITLE OF THESIS Synthetic Studies on Fukinanolide

DEGREE FOR WHICH THESIS WAS PRESENTED M. Sc.

YEAR THIS DEGREE GRANTED 1982

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

82-156

THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON FUKINANOLIDE

by

© MING KAI WONG

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
FALL, 1982

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled SYNTHETIC STUDIES ON FUKINANOLIDE submitted by MING KAI WONG in partial fulfilment of the requirements for the degree of Master of Science.

To my parents

and

my wife Fai

ABSTRACT

Ester 23, a potential precursor of fukinanolide (1), was synthesized. Photocycloaddition of enone 27, prepared in three steps from 3,4-dimethylphenol (24), and vinyl acetate gave a mixture of diastereomeric keto acetates 28 which was hydrolyzed with alkali. Thioketal formation of the resulting alcohols 29 gave a mixture of diastereomeric ketal alcohols 30. One isomer which was isolated in pure form was oxidized to give the pure ketone 31a. Oxidation of the remaining isomers afforded ketone 31a and its C-5 epimer 31b. Ring expansion of ketone 31a with ethyl diazoacetate and boron trifluoride etherate gave the desired keto ester 32, reduction of which afforded two isomeric alcohols 34a and 34b. The dehydration of the two alcohols 34a and 34b was carried out by mesylation followed by elimination. For the removal of the thioketal group, the ester thus obtained was treated with W-2 Raney nickel to give diene ester 38 which was further hydrogenated to give a mixture of two epermic esters 23a and 23b.

ACKNOWLEDGEMENTS

The author wishes to thank :

Dr. H. J. Liu for his supervision and assistance in this work and the preparation of this thesis.

Mr. R. Swindlehurst, Dr. T. T. Nakashima and their associates for recording the nmr spectra.

Dr. A. M. Hogg and his staff for running the mass spectra.

Mrs. D. Mahlov and Miss K. Tracey for the microanalyses.

The staff of the research stores and the glass blowing unit.

Mr. I. V. Oppong for his suggestions on the oral presentation of this thesis.

His wife Fai and his brother Ming Yeung for typing this thesis.

TABLE OF CONTENTS

Page

Abstract v

Acknowledgement vi

Table of Contents vii

List of Tables viii

List of Figures ix

List of Schemes x

SYNTHETIC STUDIES ON FUKINANOLIDE

Chapter Page

I Introduction 1

II Results and Discussion 12

III Experimental 33

* * *

References 50

LIST OF TABLE

Page

Table I 20

LIST OF FIGURES

Page

Formulae 1-8 3

Formulae 9-13 5

Formulae 23-26 14

Formulae 27-30 16

Formulae 31a,31b 18

Formulae 32 23

Formulae 34-37 27

Formulae 38,23a,23b 31

* * *

Figure 1 22

Figure 2 36

LIST OF SCHEMES

Page

Scheme 1 6

Scheme 2 8

Scheme 3 9

Scheme 4 10

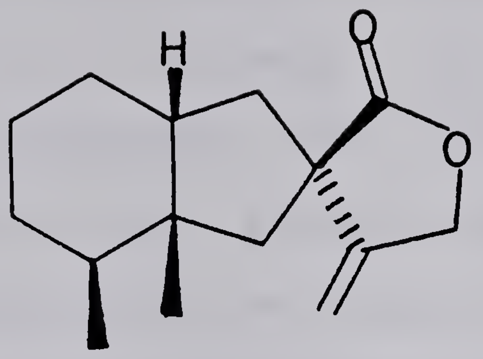
Scheme 5 25

CHAPTER I

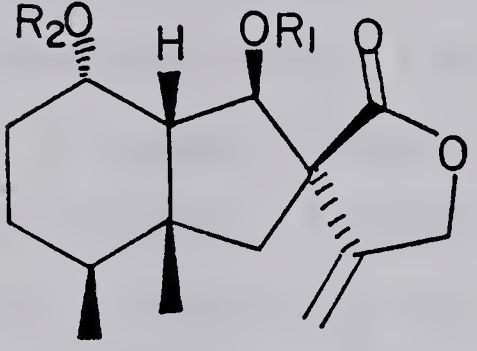
INTRODUCTION

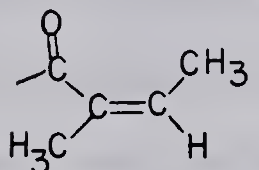
In 1968, from the flower stalks of wild butterburs, Petasites japonicus Maxim. ("Fuki" in Japanese), Naya *et al.*(1) reported the isolation of three new lactones, named fukinanolide (1), fukinolide (2) and S-fukinolide (3). Their subsequent work on the same wild plant led to the isolation of two more sesquiterpene lactones, namely dihydrofukinolide (4) and homofukinolide (5) (2, 3). At about the same time, from the bud of Petasites japonicus subsp. giganteus Kitam (local name: Bakke) indigenous to the northern part of Japan, Kitahara and his coworkers (4-7) also isolated compound 1-3, which were named bakkenolide-A, -B and -C respectively, along with three closely related lactones, bakkenolide-D (6) and -E (7) and 1,9-dihydroxybakkenolide-A (8). Since then, fukinanolide (bakkenolide-A) (1) was also isolated from other strains of Petasites japonicus (8-10) and from some South African Senecio species (11).

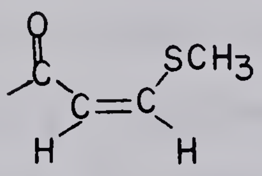
The structure and absolute configuration of fukinanolide (1) (2,3,4,7) were established independently by the afore-mentioned two groups by a combination of spectroscopic and chemical methods including its correlation with fukinone (9) (12, 13) of known structure and absolute

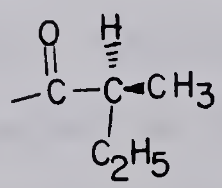


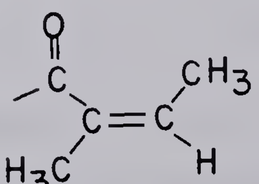
1

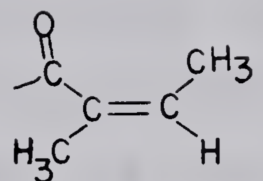


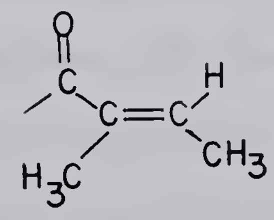
2 R_1 = Ac ; R_2 =

O
C
CH3
C=C
H3C
H

3 R_1 = Ac ; R_2 =

O
C
SCH3
C=C
H
H

4 R_1 = Ac ; R_2 =

O
H
C
C
CH3
C2H5

5 R_1 = R_2 =

O
C
CH3
C=C
H3C
H

6 R_1 = H ; R_2 =

O
C
CH3
C=C
H3C
H

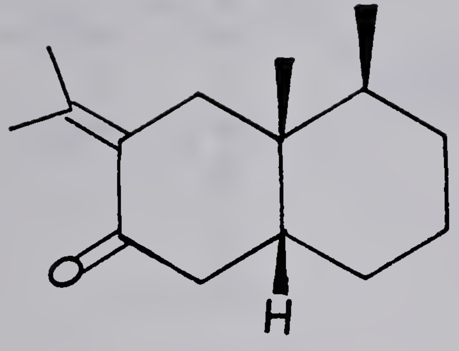
7 R_1 = Ac ; R_2 =

O
C
H
C=C
H3C
CH3

8 R_1 = R_2 = H

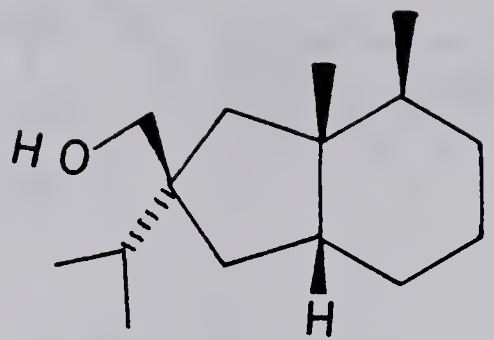
configuration (12, 13) *via* fukinan-8-ol (10) (3) and its degradation to the known perhydroindanone derivative 11 (7).

Fukinanolide (1) belongs to a new group of sesquiterpenoids possessing the novel carbon skeletion of fukinane (12). Since many sesquiterpenoids based on the eremophilane framework (13) were also found (14) in the same genus, *Petasites*, it is conceivable that the fukinane (12) skeleton arises biogenetically from that of eremophilane (13) involving, in a formal sense, the migration of a carbon-carbon bond (C8-C9 to C7-C9) (15). With respect to the bond in question, Kitahara *et al*. (16, 17, 18)further suggested that its migration could be facilitated by epoxidation of an intermediate such as fukinone (9) followed by a Favorskii-type rearrangement. Interestingly, the first preparation of fukinane (12) skeleton (3) was successfully carried out based on the biogenetic consideration. In the synthesis, fukinone (9) was used as the starting material which was converted to fukinan-8-ol (10) and finally to fukinane (12) according to Scheme 1.

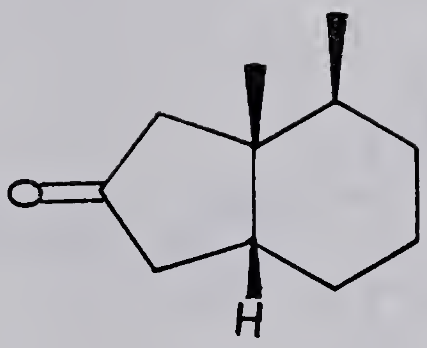
The first total synthesis of fukinanolide (1) in racemic form was reported in 1973 by Evans and Sims (19). The synthetic approach was based on their earlier work on the stereoselectivity of a [2,3]sigmatropic rearrangement (20). The key operation of the synthesis was the sodium hydride induced [2,3]sigmatropic rearrangemnt of compound 14



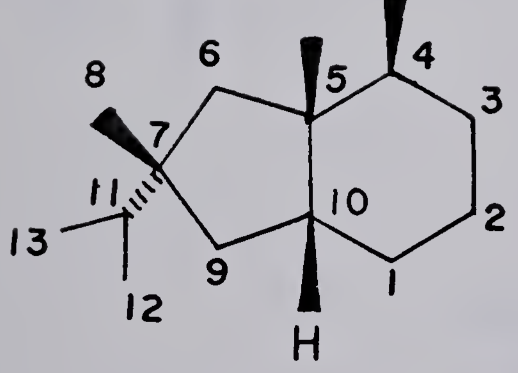
9



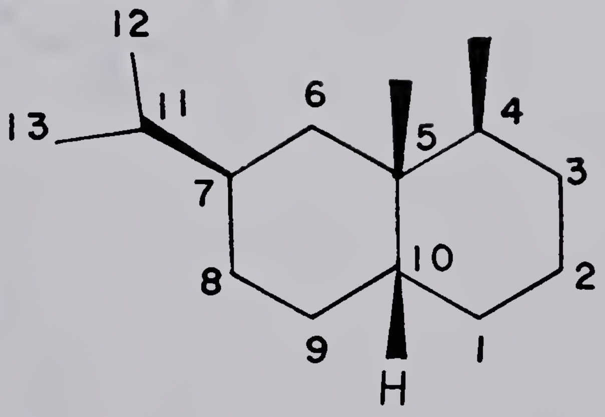
10



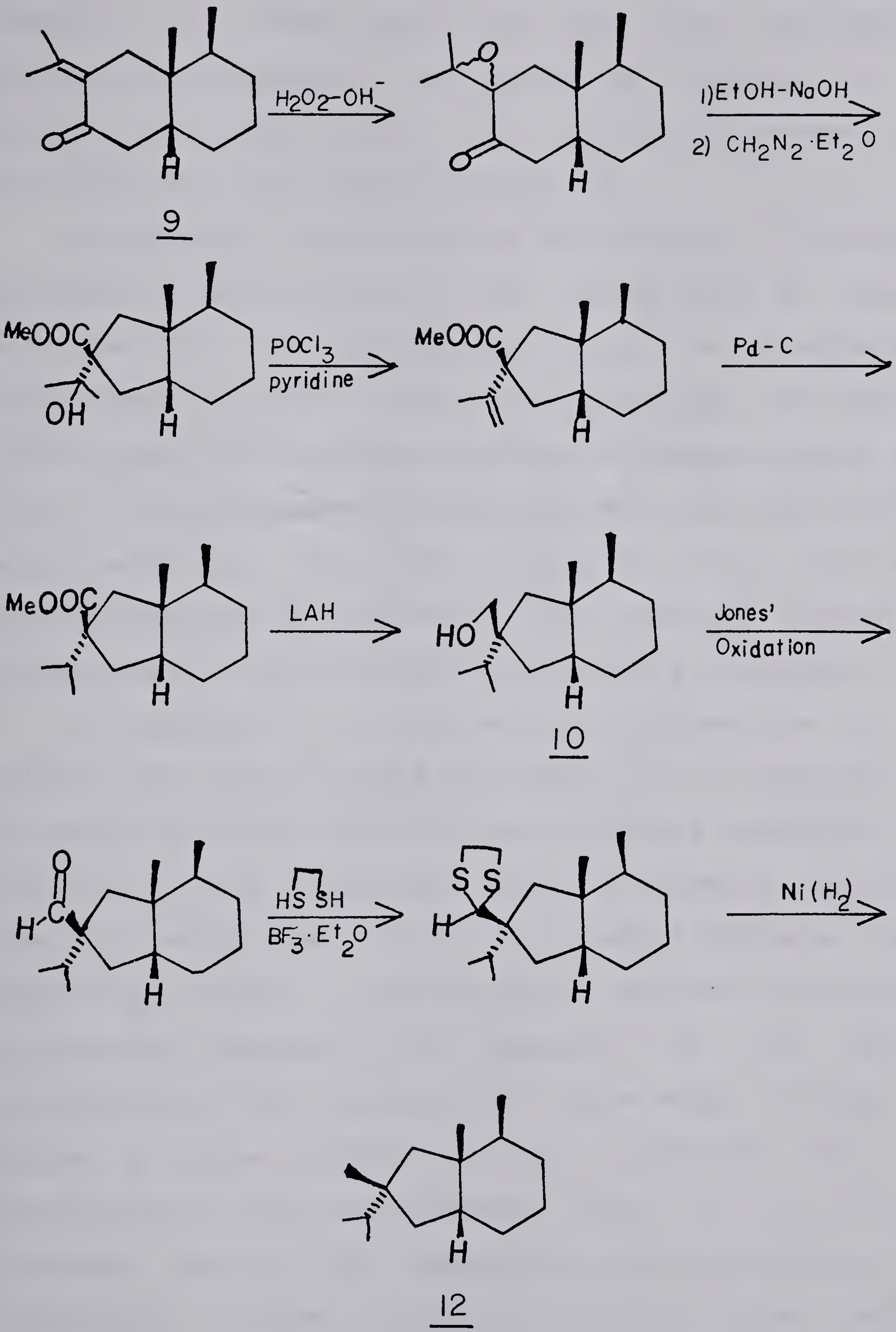
11


8
6
5
4
3
7
11
10
2
13
9
1
12
H

12


12
13
11
6
5
4
3
7
10
8
2
9
1
H

13

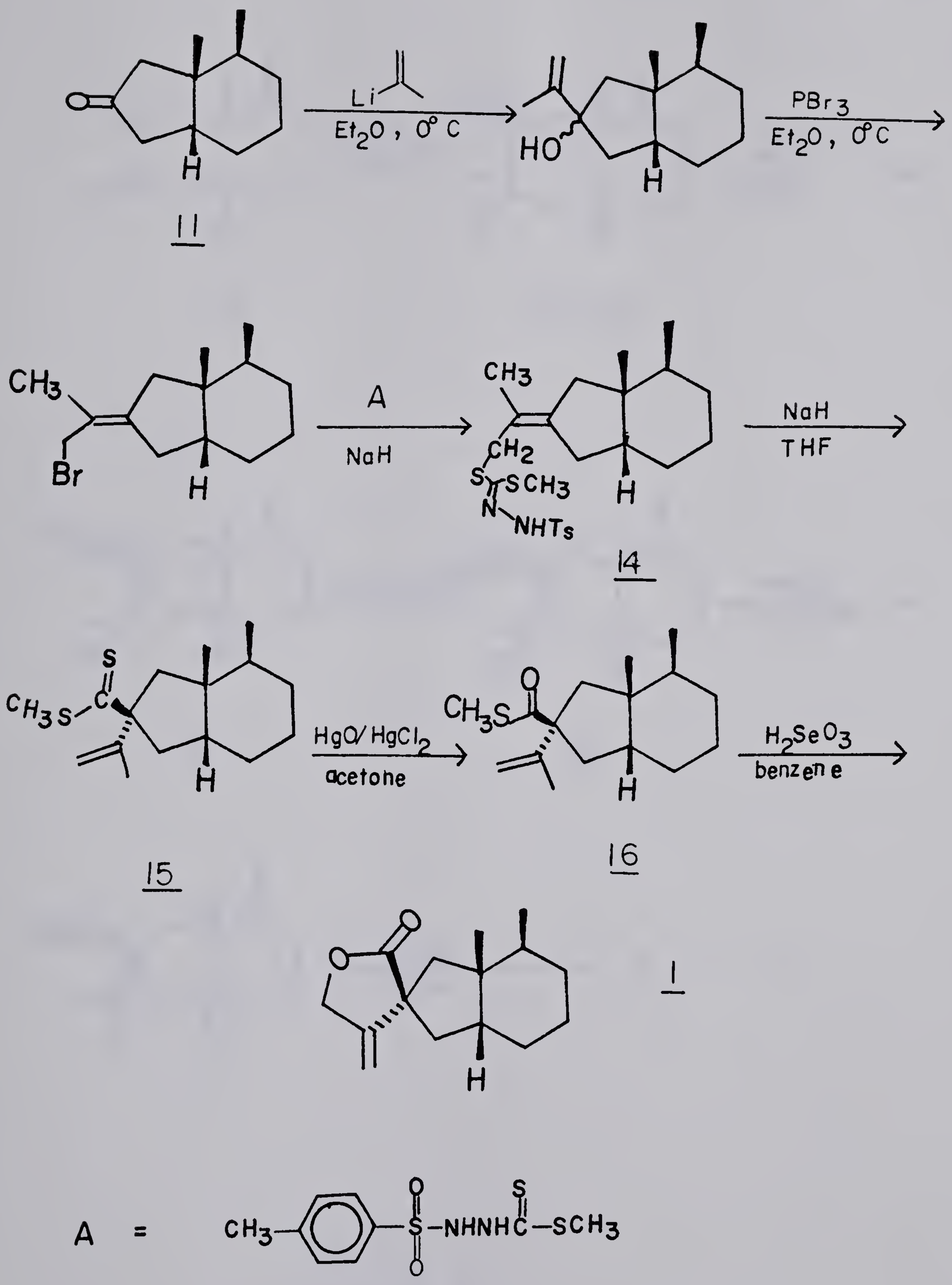

H
9
H₂O₂-OH⁻
O
1)EtOH-NaOH
2) CH₂N₂·Et₂O
MeOOC
OH
POCl₃
pyridine
Pd-C
LAH
HO
Jones' Oxidation
10
O
H
HS SH
BF₃·Et₂O
S S
Ni(H₂)
12

SCHEME I

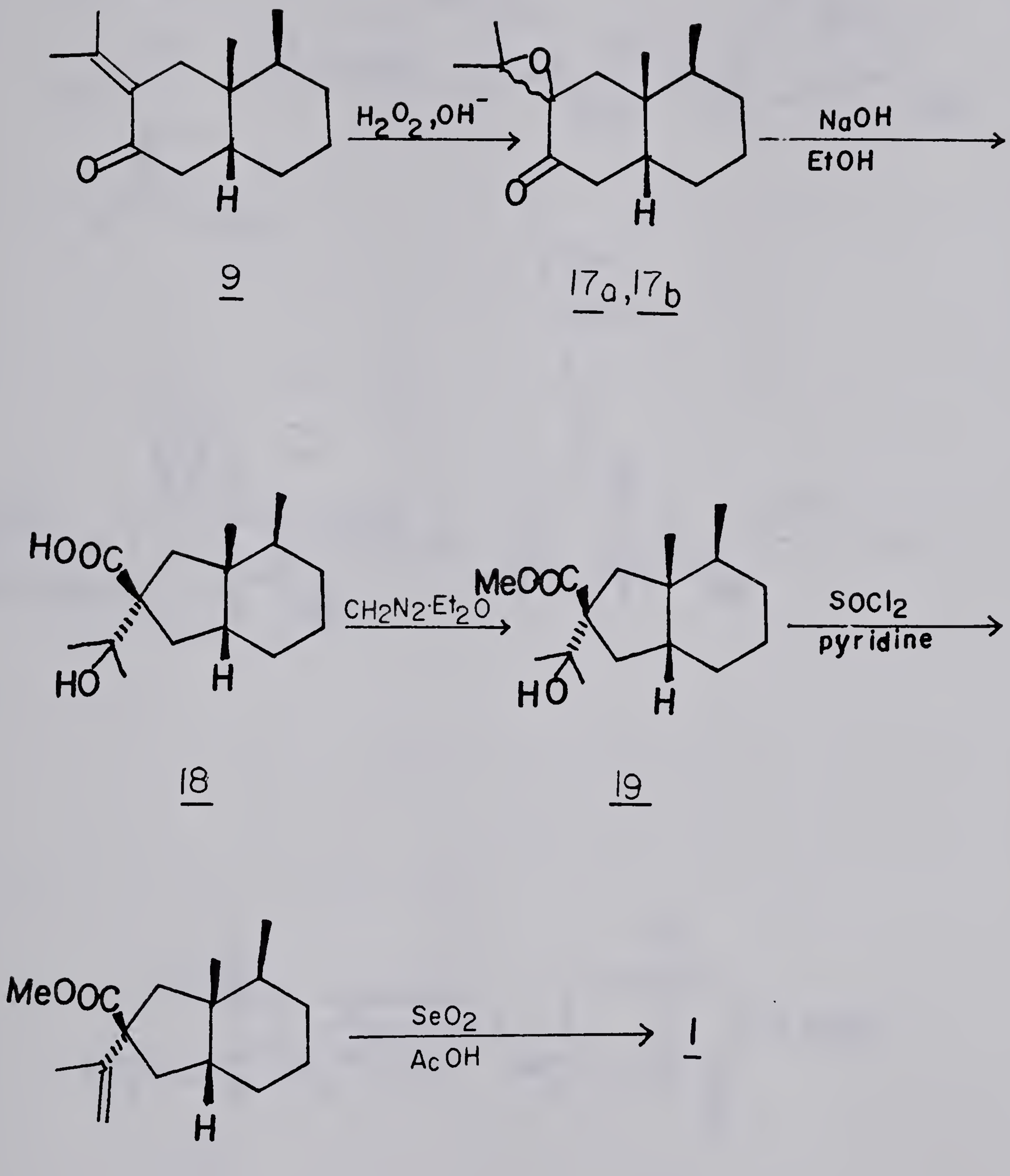
prepared in three steps from the known hydrindanone derivative 11 (Scheme 2), to compound 15. Hydrolysis of 15 afforded the thiol ester (16) which on treatment with selenious acid gave (±)fukinanolide (1).

Concurrently, starting from fukinone (9), a biomimetic synthesis of fukinanolide (1) was accomplished by Hayashi and coworkers (21). Epoxidation of fukinone (9) afforded a diastereomeric mixture of epoxides 17a and 17b. Treatment of this mixture with sodium hydroxide in aqueous ethanol gave rise to the rearrangement product 18 which was esterified to methyl ester (19). Dehyration of 19 with thionyl chloride in pyridine followed by oxidation with selenium dioxide in aqueous acetic acid afforded fukinanolide (1) (Scheme 3).

Our approach to the synthesis of fukinanolide (1) is based on the general method developed in this laboratory for the synthesis of the hydrindanonecarboxylate system(22). As illustrated with isophorone (20) in Scheme 4, the method involves the construction of a bicyclo[4.2.0]octane system (20 ⟶ 21) using a photochemical approach and the boron trifluoride catalyzed ring expansion of the derived cyclobutanone with diazoacetate (21 ⟶ 22). During the course of these studies, it was observed that the homologation of the cyclobutanone rings (e.g. 21 ⟶ 22) proceeded with a high degree of regioselectivity and consistency. Wherever applicable, products formed resulted

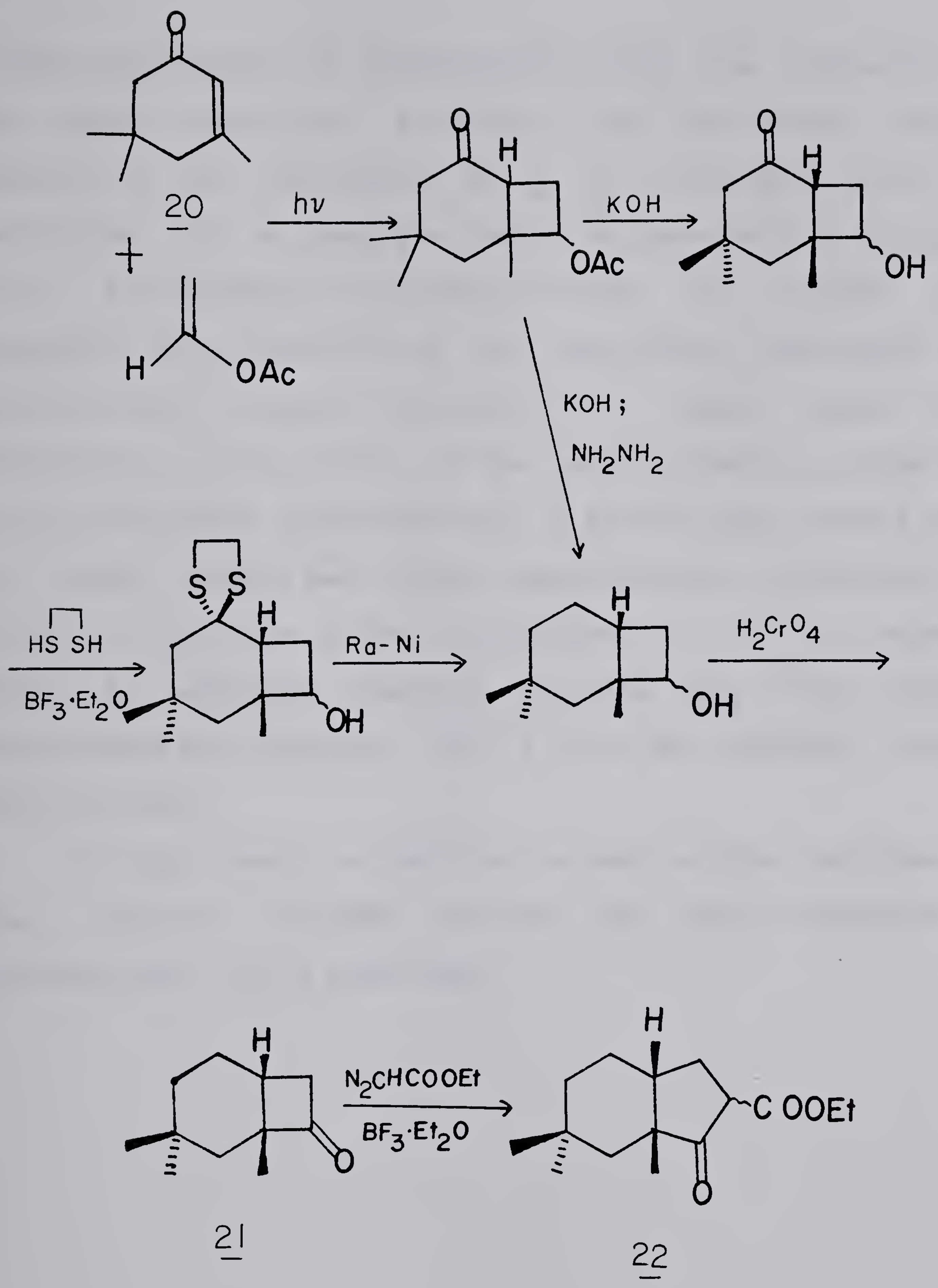

11
Li
Et$_2$O , 0° C
HO
H
PBr$_3$
Et$_2$O , 0° C
CH$_3$
Br
A
NaH
CH$_3$
CH$_2$
S
SCH$_3$
N
NHTs
14
NaH
THF
S
CH$_3$S
C
HgO/HgCl$_2$
acetone
15
O
CH$_3$S
16
H$_2$SeO$_3$
benzene
1
A = CH$_3$–C$_6$H$_4$–SO$_2$–NHNHC(=S)–SCH$_3$

SCHEME 2



9
H_2O_2, OH^-
17a, 17b
NaOH
EtOH
HOOC
HO
H
18
$CH_2N_2 \cdot Et_2O$
MeOOC
HO
19
$SOCl_2$
pyridine
MeOOC
SeO_2
AcOH
1

SCHEME 3


20
hν
KOH
KOH ;
NH2NH2
HS SH
BF3·Et2O
Ra-Ni
H2CrO4
21
N2CHCOOEt
BF3·Et2O
22
OAc
OH
C OOEt

SCHEME 4

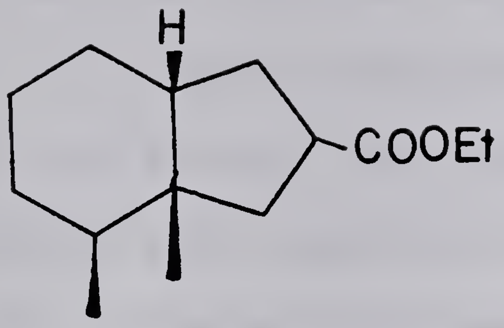
either exclusively or predominantly from the migration of the less substituted α-carbon. The application of this method to the synthesis of 1 is straightforward in principle. By a suitable choice of the starting material, i.e. 3,4-dimethyl-2-cyclohexen-1-one, it should make possible the construction of the parent hydrindane ring system of the target molecule in a simple manner with concomitant incorporation of the required methyl groups and, with predictable regiochemistry, a β-keto ester moiety which is highly useful for further manipulation. In addition, by virtue of the mode of the transformation, it is expected that a complete control of the cis ring juncture stereochemistry required for 1 can be achieved without difficulties.

In this thesis, a detailed account of the progress in the studies directed towards the total synthesis of fukinanolide (1) is described.

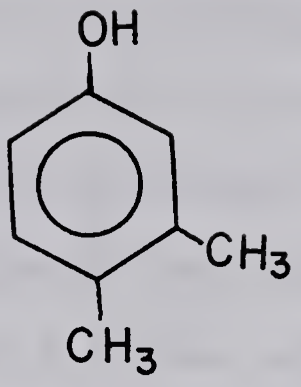
CHAPTER II

RESULTS AND DISCUSSION

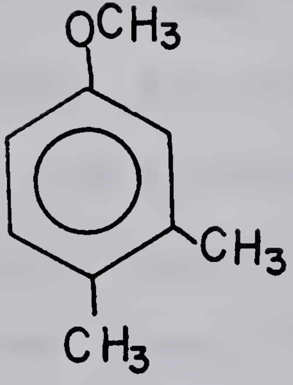
The synthesis of ester 23 , a potential precursor of fukinanolide (1), made use of 3,4-dimethylphenol (24) as the starting material for the obvious presence of the two methyl substituents which are also found in the natural product. Methylation of phenol 24 with methyl iodide in refluxing acetone in the presence of potassium carbonate gave the corresponding anisole 25 in 87% yield. Birch reduction (23) of the anisole 25 with lithium in ammonia in the presence of t-butyl alcohol afforded the enol ether 26 which, without purification, was treated with aqueous hydrochloric acid to give 3,4-dimethyl-2-cyclohexen-1-one (27). The yield was 66% in two steps. The infrared spectrum showed the presence of a conjugated ketone by absorption bands at 1675 and 1622 cm^{-1}. The olefinic proton appeared as a singlet at δ 5.78 in the nmr spectrum. Photocycloaddition (24, 25) of 3,4-dimethyl-2-cyclohexen-1-one (27) with vinyl acetate proceeded *via* a head-to-tail fashion to give a diastereomeric mixture of keto acetates 28 in 75% yield. In the nmr spectrum, three singlets due to the acetoxy group appeared in the δ 2 region indicating the presence of at least three diastereomers. No attempt was made to separate them as two of the chiral centres (marked with *) present in the molecule would be either epimerized or destroyed in the



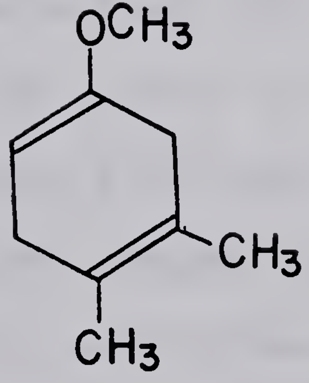
23



24

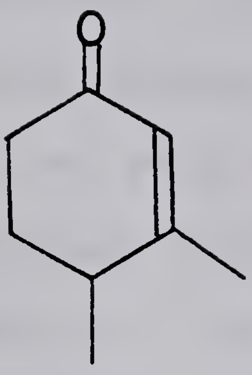

OCH3
CH3
CH3

25

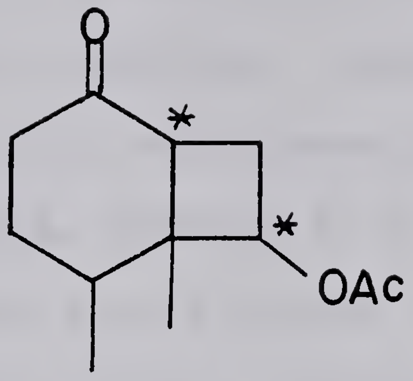

OCH3
CH3
CH3

26

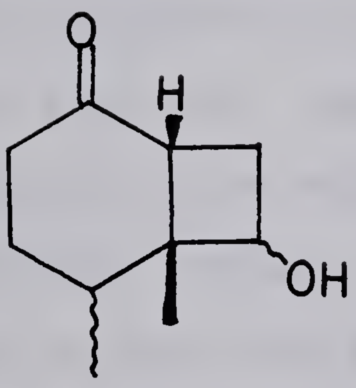
later stages. Hydrolysis of the mixture of keto acetates 28 with aqueous sodium hydroxide in methanol at reflux afforded the corresponding alcohol 29 in 76% yield. The nmr spectrum was rather complex due to the diastereomeric nature of the mixture. The methine hydrogen adjacent to the hydroxyl group appeared as a complex multiplet at about δ 4.0, which was integrated to one proton. The presence of six methyl protons were indicated by the integration of signals observed in the δ 1 region. The infrared spectrum showed a strong absorption at 3238 cm^{-1} characteristic for the hydroxyl group. Based on the previous observations (27), it has been well established that the *trans* ring juncture in a bicyclo[4.2.0]octan-2-one system is readily epimerized to give the thermodynamically more stable *cis* form upon treatment with base. Therefore a *cis* ring juncture could readily be assigned. The isomeric mixture of keto alcohols 29 was thioketalized (28, 29) with 1,2-ethanedithiol in the presence of boron trifluoride etherate and the corresponding thioketals 30 were obtained in 80% yield. Upon purification by column chromatography on silica gel, one isomer which was faster-moving was isolated in crystalline form (m.p. 88-90 °C) and the rest as a mixture in the ratio of 1:9. The infrared spectrum of the pure ketal alcohol displayed a strong absorption band at 3320 cm^{-1} and the absence of any band at the region of 1800-1600 cm^{-1} in agreement with the assignment of its gross



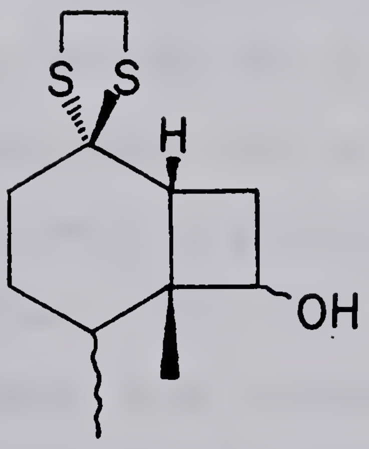
27



28



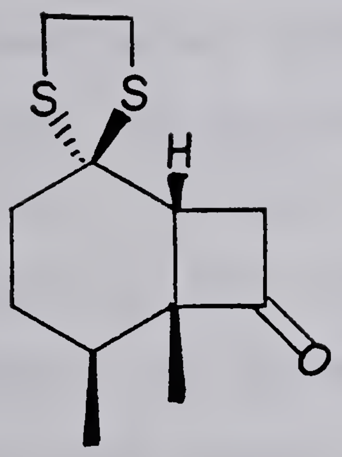
29



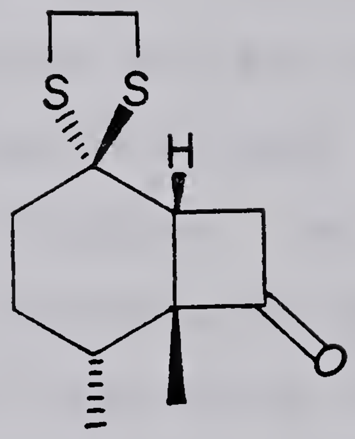
30

structure. The nmr spectrum showed a triplet at δ 4.06 for the methine proton adjacent to the hydroxyl group and a multiplet at δ 3.30 for the four methylene protons of the thioketal grouping. A singlet at δ 1.22 and a doublet with a coupling constant of 6 Hz at δ 1.12 were also observed for the two methyl groups. The mass spectrum, which gave a molecular ion peak at m/e 244.0954, and elemental analysis were in agreement with the molecular formula $C_{12}H_{20}OS_2$. The isomeric mixture was obtained as a pale yellow liquid, the infrared spectrum of which showed a strong absorption band at 3396 cm^{-1} for the hydroxyl group. The isomeric nature of the mixture was confirmed by the nmr spectrum which displayed a group of complex signals at δ 4.32 - 3.74 for a total of one hydrogen atom and this could be assigned to the methine proton adjacent to the hydroxyl group. Two methyl groups also appeared in a complex pattern at δ 1.16 - 0.82. The mass spectrum showed a molecular ion at m/e 244.0951 corresponding to the molecular formula $C_{12}H_{20}OS_2$.

Modified Moffatt oxidation (30) was carried out separately on the single isomer and the isomeric mixture. Upon treatment with dimethylsulfoxide and acetic anhydride at 5 °C for 24 hours, the single alcohol gave the corresponding ketone 31a (90% yield) which was purified by column chromatography on silica gel and recrystallized from petroleum ether to a constant melting point of 73 - 74 °C.



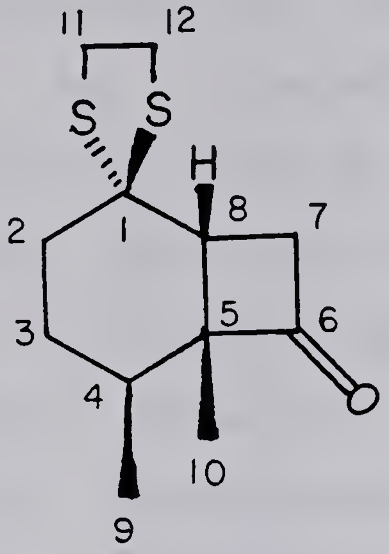
31a



31b

The infrared spectrum showed a strong absorption at 1776 cm^{-1} characteristic of a four-membered ring ketone carbonyl. In the nmr spectrum the thioketal protons appeared as a multiplet at δ 3.40. Methyl signals were observed as a sharp singlet at δ 1.28 and a doublet at δ 1.o2 with a coupling constant of 6 Hz. The mass spectrum which displayed a molecular ion peak at m/e 242.0789 and the elemental analysis were also consistent with the structural assignment. The purity of the compound was confirmed by cmr spectroscopy consisting of only twelve peaks (Table I). Similar oxidation of the isomeric mixture with dimethylsulfoxide and acetic anhydride gave two inseparable ketones 31a and 31b in a 1:2 ratio and in a total yield of 67%. The infrared spectrum displayed two carbonyl absorptions at 1780 and 1760 cm^{-1} indicating the presence of two isomers. In agreement with this observation was the nmr spectrum which showed two sets of signals in a ratio of 1:2. The minor set was found to be identical with that observed for the pure ketone 31a obtained previously. The major set which could be readily attributed to the isomeric ketone 31b consisted of a singlet at δ 3.36 for the four methylene protons of the thioketal group, a methyl singlet at δ 1.12 and a methyl doublet at δ 0.94 with a coupling constant of 7 Hz. The two ketones 31a and 31b were found to recrystallize together from petroleum ether (m.p. 104 - 106 °C). A single

Table I. ^{13}Cmr Spectrum (δ) of Ketone 31a


11
12
S
S
H
8
7
2
1
5
6
3
4
10
9

31a

C - 1	40.7
C - 2	33.0
C - 3	28.3
C - 4	34.1
C - 5	48.6
C - 6	213.6
C - 7	47.0
C - 8	38.0
C - 9	16.6
C - 10	21.8
C - 11	66.4, 67.4
C - 12	

crystal X-ray diffraction revealed that the crystal was composed of one part of 31a and two part of 31b as well as the stereochemistry of these two ketones (Figure I).

To facilitate further discussion, a summary of the results so far obtained is deemed appropriate. Photocycloaddition of enone 27, prepared in three steps from 3,4-dimethylphenol (25), and vinyl acetate gave a mixture of diastereomeric keto acetates 28 which was hydrolyzed with alkali. Thioketal formation of the resulting alcohols 29 gave a mixture of diastereomeric ketal alcohols 30. One isomer which was isolated in pure form was oxidized to give the pure ketone 31a. Oxidation of the remaining isomers afforded ketone 31a and its C-5 epimer 31b, the separation of which has yet to be accomplished.

Further exploration was carried out using the pure ketone 31a. Ring expansion of ketone 31a with ethyl diazoacetate and boron trifluoride etherate (31, 32) gave exclusively the desired keto ester 32 in 51% yield. Keto ester 32 was first obtained as a pink oil and on standing it crystallized. Removal of the crystals led to further aggregation of crystals in the mother liquid. By repetition of this process, virtually all of keto ester 32 was isolated as white crystals (m.p. 79 - 81 °C). Interestingly, the nmr spectrum showed two sets of signals for the original oily product and only one set of signals for the crystalline

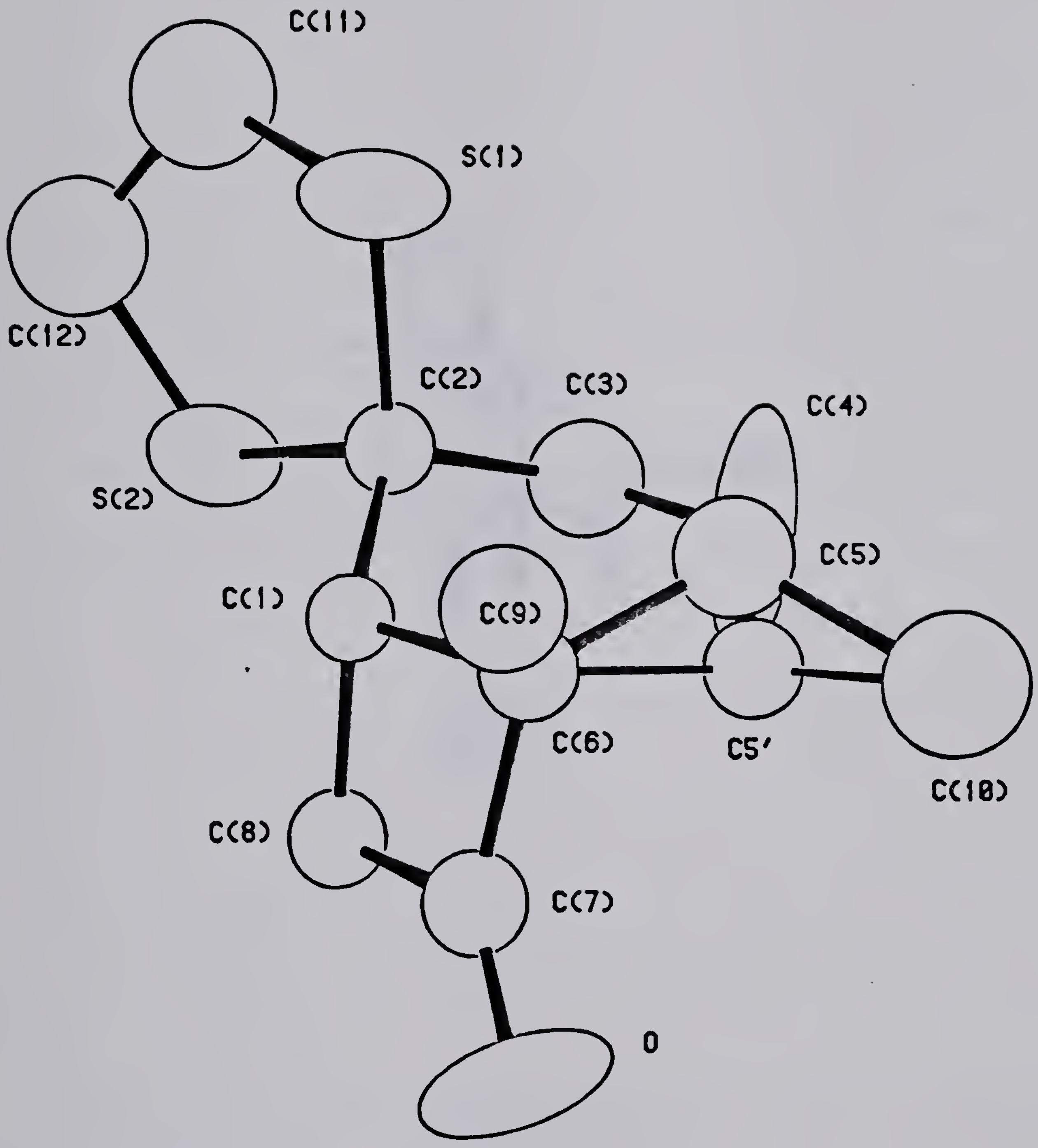
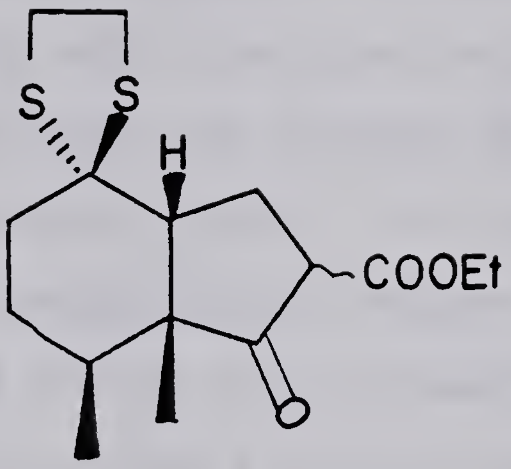

C(11)
S(1)
C(12)
C(2)
C(3)
C(4)
S(2)
C(5)
C(1)
C(9)
C(6)
C5'
C(10)
C(8)
C(7)
O

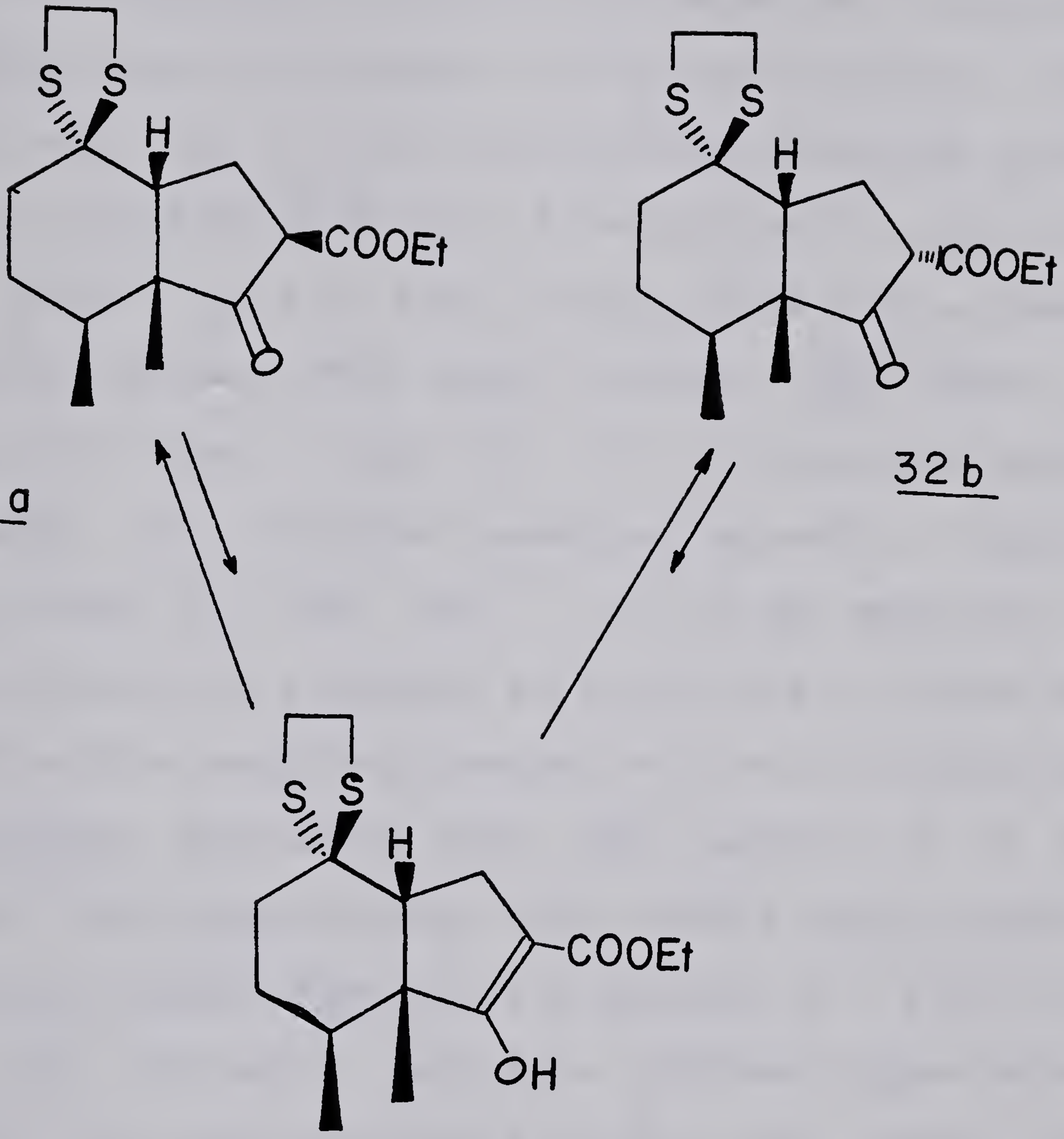
Figure 1. Perpective view of ketones 31a and 31b showing the atom numbering scheme. The atoms are represented as 50% thermal ellipsoids.



32

compound. This phenomenon could be logically explained as follows. In principle, the ring expansion reaction could lead to the formation of two epimeric keto esters 32a and 32b, one of which readily crystallized on standing. Since these two epimers are readily interconvertable *via* the enol form 33 (Scheme 5), removal of the crystalline epimer shifts the equilibrium resulting in its further formation in the mother liquid. The following spectral data of the crystalline keto ester were consistent with its structural assignment of 32a or 32b. The infrared spectrum displayed a five-membered ring ketone carbonyl and ester carbonyl at 1740 and 1722 cm^{-1} respectively. The nmr spectrum showed a two proton quartet at δ 4.22 with a coupling constant of 7 Hz and a three proton triplet at δ 1.30 also with a coupling constant of 7 Hz due to the carbethoxy group. The thioketal group gave a four proton singlet at δ 3.32 and methyl groups appeared as a singlet at δ 1.32 and a doublet at δ 1.15 with a coupling constant of 6 Hz. The mass spectrum showed a molecular ion peak at m/e 328.1167 confirming the molecular formula $C_{16}H_{24}O_3S_2$.

Reduction of the crystalline keto ester 32a/32b with sodium borohydride in ethanol (33) at 0 °C for seven hours afforded two isomeric alcohols 34a and 34b in 3:4 ratio and in a total yield of 76%. The minor isomer 34a which was obtained as an oil showed the following spectral data. In


COOEt
COOEt
COOEt
S
S
H
OH

32a

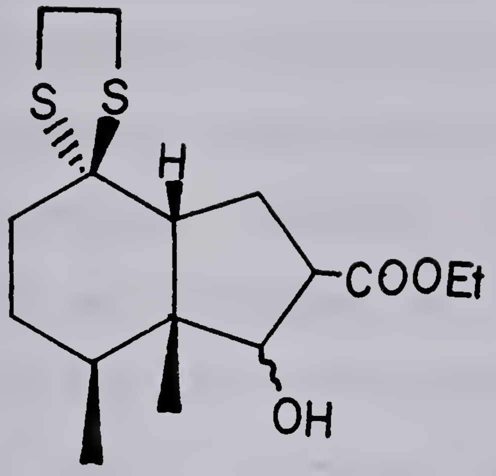
32b

33

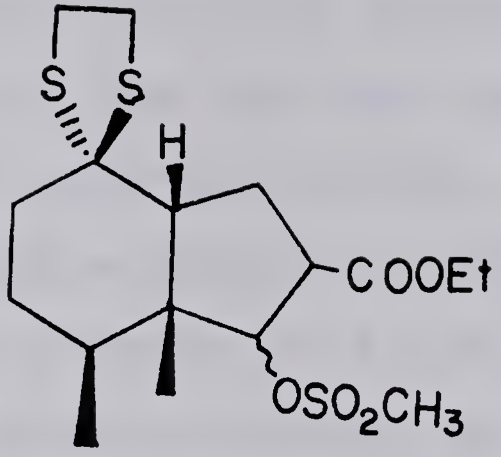
SCHEME 5

the infrared spectrum, a strong hydroxyl absorption appeared at 3471 cm^{-1}. In the nmr spectrum, a quartet at δ 4.22 and a triplet at δ 1.30 with the same coupling constant of 7 Hz were observed for the carbethoxy group. The methine proton adjacent to the hydroxyl group was displayed as a doublet at δ 4.10 with a coupling constant of 5 Hz. The hydroxyl group gave a singlet at δ 4.03. The thioketal methylene protons appeared as a singlet at δ 3.30. A doublet at δ 1.15 with a coupling constant of 6 Hz and a singlet at δ 0.98 accounted for the methyl protons. The major alcohol 34b which was obtained as crystals (m.p. 99 - 101 °C) displayed similar spectral data. the infrared spectrum showed a hydroxyl absorption band at 3505 cm^{-1}. In the nmr spectrum, the carbethoxy group gave a quartet at δ 4.20 and a triplet at δ 1.29, each with a coupling constant of 7 Hz. A singlet at δ 4.16 overlapping partially with the quartet at δ 4.20 represented the hydroxyl group. The methine proton adjacent to the hydroxyl group appeared as a doublet (J = 5 Hz) at δ 4.12 and the thioketal methylene protone appeared as a singlet at δ 3.32. The two methyl groups were shown as a doublet (J = 6 Hz) at o 1.22 and a singlet at δ 1.10. The mass spectra of both alcohols shown in each case a molecular ion peak consistent with the molecular formula $C_{16}H_{26}O_3S_2$.

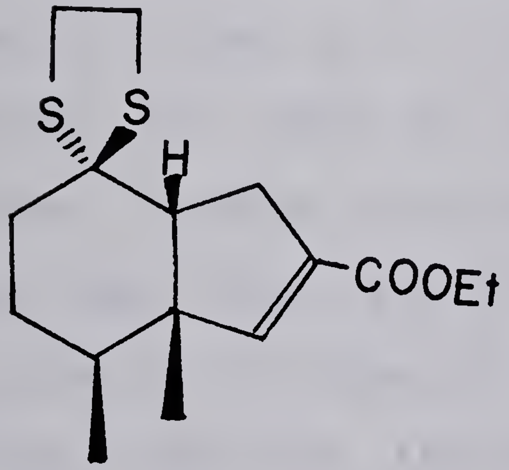
The dehydration of the two alcohols 34a and 34b was carried out individually by a two-step sequence: mesylation



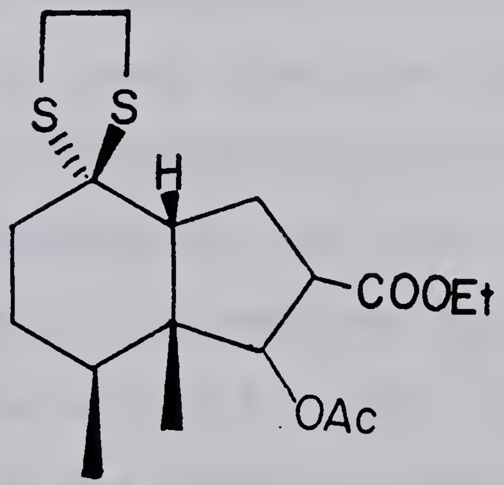
34 a
34 b



35 a
35 b



36



37

followed by elimination. Mesylation of the minor alcohol 34a with methanesulfonyl chloride in pyridine in the presence of a catalytic amount of 4-N ,N-dimethylaminopyridine afforded mesylate 35a in 81% yield. The infrared spectrum showed the ester carbonyl absorption at 1734 cm^{-1} and the absence of the hydroxyl absorption band. In the nmr spectrum, the methine proton adjacent to the methanesulfonyloxy group appeared as a doublet at δ 5.16 with a coupling constant of 4 Hz and the carbethoxy group gave a quartet at δ 4.20 and a triplet at δ 1.31 with the same coupling constant of 7 Hz. The thioketal methylene protons were displayed as a singlet at δ 3.29. The methyl protons of the methanesulfonyloxy group appeared as a sharp singlet at δ 3.08. The other methyl groups were observed as a singlet at δ 1.17 and a doublet (J = 6Hz) at δ 1.15. The mass spectrum gave a molecular ion peak at m/e 408.1105 characteristic of the molecular formula $C_{20}H_{24}O_5S_2$. Mesylation of the major alcohol 34b gave 35b in 74% yield. Its spectral data were quite similar to those of the above mesylate. The infrared spectrum indicated the absence of the hydroxyl absorption. In the nmr spectrum, the methine proton adjacent to the methanesulfonyloxy group appeared as a doublet at δ 5.07 with a coupling constant of 4 Hz. The methyl protons of the methanesulfonyl group appeared as a singlet at δ 3.10. The mass spectrum showed a molecular ion peak at m/e 408.1099 in

agreement with the required molecular formula $C_{20}H_{24}O_5S_2$.

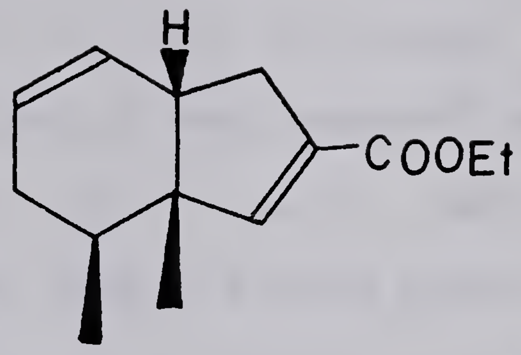
Mesylate 35a was treated with sodium hydride in 1,2-dimethoxyethane at 0 °C for one hour; compound 36 was obtained in 99% yield. The infrared spectrum displayed absorption bands at 1714 and 1614 cm^{-1} for the ester group and the carbon-carbon double bond repectively. In the nmr spectrum, the olefinic proton appeared as a singlet at δ 6.57. The carbethoxy protons appeared as a quartet at δ 4.22 and a triplet at δ 1.32 with the same coupling constant of 7 Hz. A multiplet at δ 3.25 was indicative of the presence of the thioketal methylene protons. The methyl protons appeared as a singlet at δ 1.33 and a doublet at δ 0.98 with a coupling constant of 6 Hz. The mass spectrum displayed a molecular ion peak at m/e 312.1221 in agreement with the structural assignment for $C_{16}H_{24}O_2S_2$. Similar treatment of mesylate 35b with sodium hydride gave the same compound 36.

The dehydration of 34b was also carried out by acetylation followed by elimination. Alcohol 34b, on treatment with acetic anhydride in pyridine at room temperature for 24 hours, afforded the corresponding acetate 37 in 99% yield. The infrared spectrum showed the absence of the hydroxyl absorption band. The two ester carbonyls were displayed as a broad absorption band at 1736 cm^{-1}. In the nmr spectrum, the methine proton adjacent to the acetoxy group appeared as a doublet at δ 5.06 with a coupling

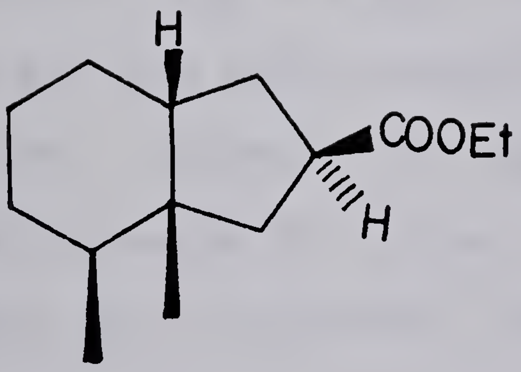
constant of 4 Hz, and the methyl protons of the acetate appeared as a singlet at δ 2.10. The remaining signals were also characteristic of the compound. The carbethoxy group appeared as a quartet at δ 4.18 and a triplet at δ 1.27 with the same coupling constant of 7 Hz. A doublet at δ 1.05 with a coupling constant of 6 Hz and a singlet at δ 1.15 represented the two methyls. Treatment of the acetate 37 with sodium hydride in 1,2-dimethoxyethane at 0 °C for one hour, gave compound 36 in 99% yield.

Acetylation of alcohol 34a was also attempted but without success. In this case, starting material was recovered.

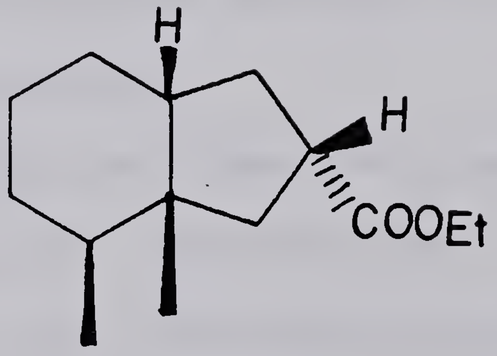
For the removal of the thioketal group (34, 35), ester 36 was treated with W-2 Raney nickel (36) in benzene at room temperature for five days. The product 38 thus obtained in 72% yield showed, in the infrared spectrum, an olefinic absorption band at 1630 cm^{-1} and an ester carbonyl at 1715 cm^{-1}. The nmr spectrum showed the absence of any signals at δ 4 - 3 indicating the complete removal of the thioketal group and two multiplets centered at δ 6.74 and δ 5.55 (2H) due to the olefinic protons. The carbethoxy group appeared as a quartet (J = 7 Hz) at δ 4.18 and a triplet (J = 7 Hz) at δ 1.39 and the methyl groups were displayed as a singlet at δ 1.10 and a doublet (J = 6 Hz) at δ 1.04. The mass spectrum gave a molecular ion peak at m/e 220.1461 in



38



23a



23b

agreement with the molecular formula $C_{14}H_{20}O_2$.

The diene ester 38 was further hydrogenated in ethanol with freshly prepared W-2 Raney-nickel under a hydrogen atmosphere for 24 hours. A mixture of two epimeric esters 23a and 23b was obtained in 97% yield. The infrared spectrum of the mixture displayed a strong absorption band at 1734 cm^{-1} characteristic of the saturated ester. In the nmr spectrum, the carbethoxy group appeared as a quartet at δ 4.16 and a triplet at δ 1.28, each having a coupling constant of 7 Hz. The methyl groups gave two sets of signals integrated to a ratio of 2:3 indicating the presence of two epimers. The major set was composed of a doublet (J = 6 Hz) at δ 0.88 and a singlet at δ 0.98, while a doublet (J = 6 Hz) at δ 0.88 and a singlet at δ 1.01 were observed for the minor one. Since the hydrogenation of ester 38 is expected to occur preferentially from the less hindered convex side, structures 23a and 23b could be tentatively assigned to the minor and the major components respectively.

The synthesis of 23a and 23b concludes our present advance towards the total synthesis of fukinanolide (1). Methods are currently under study for the construction of the remaining spiral β-methylene-γ-lactone system.

CHAPTER III

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Nicolet 7-199 FT-IR spectrophotometer and were obtained on solutions in chloroform. Proton nuclear magnetic resonance (nmr) spectra were recorded on a Varian HA-100/Digilab spectrometer and were obtained on solutions in deuterated chloroform with tetramethyl silane as internal standards. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Mass spectra (ms) were recorded using A.E.I. Model MS50 mass spectrometer. Elemental analysis were performed by the microanalytcal laboratory of this department. Carbon 13 nuclear magnetic resonance (cmr) spectrum was recorded on a Bruker HFX-90/Nicolet 1085 system in deuterated chloroform with tetramethyl silane as internal standard. The X-ray analysis was performed with an Enraf-Nonius CAD 4 automated diffractmeter.

Materials

Benzene, diethyl ether (ether) and 1,2-dimethoxyethane (DME) were freshly distilled over lithium aluminum hydride.

Pyridine was distilled over barium oxide and stored over potassium hydroxide pellets. Ethanol was refluxed over magnesium turnings at elevated temperature for 2 hr. and distilled. Boron trifluoride etherate was distilled over calcium hydride according to the procedure of Brown (37). Merck Kieselegel G (type 60) silica gel was used for thin layer chromatography. Silica gel 60-120 mesh was used as absorbent for column chromatography. Silica gel 60, 0.040-0.063 mm particle size, 230-400 mesh ASTM was used as absorbent for flash chromatography (38). Nitrogen and argon were passed through a purification train of Fieser's solution, concentrated sulfuric acid and potassium hydroxide pellets.

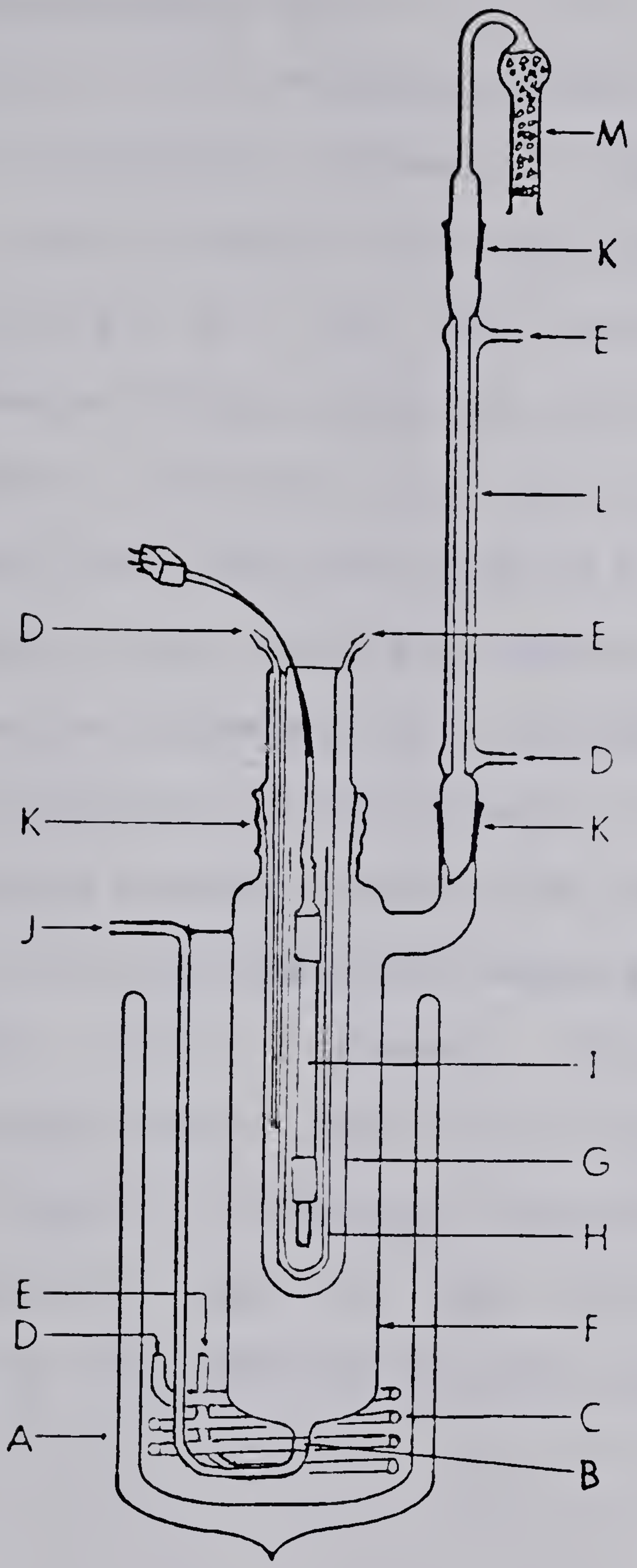


Fig. 2. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

3,4-Dimethylanisole (25)

A mixture of 3,4-dimethylphenol (24) (104.44 g, 0.86 mol) and potassium carbonate (156 g, 1.13 mol) in acetone (625 ml) was stirred at room temperature for 3 hr. Methyl iodide (183.81 g, 1.30 mol) was added and the resulting mixture heated under reflux for 16 hr. Water (500 ml) was added. After stirring at room temperature for 6 hr, the mixture was extracted with ether (4 X 300 ml). The extracts were washed with saturated aqueous sodium chloride, dried with magnesium sulfate, and filtered. Evaporation of the solvent followed by distillation of the crude oily product under reduced pressure using a 25 cm Vigreux column afforded 25.19 g of the starting material and 76.61 g (87% yield based on the consumed starting material) of 3,4-dimethylanisole (25): b.p. 64-66°C/2 Torr; ir ($CHCl_3$) 3010 and 1606 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 6.93-6.42 (m, 3H, aromatic), 3.60 (s, 3H, CH_3O-) and 2.12 (s, 6H, 2 X -CH_3); ms M^+ 136.0888 (Calcd. for $C_9H_{12}O$: 136.0889).

3,4-Dimethyl-2-cyclohexen-1-one (27)

At -78°C, a solution of 3,4-dimethylanisole (25). (76.61 g, 0.57 mol) in ether (500 ml) and *t*-butyl alcohol (500 ml) was added over a period of 50 min. to freshly distilled ammonia (1.1 l) under a nitrogen atmosphere.

Lithium (64.35g, 9.3 g-atom) was added in small portions (ca. 2 g each) over a period of 40 min. The resulting blue solution was stirred for 5 hr. after which period the blue color was discharged. Methanol (500 ml) was added dropwise and the ammonia was allowed to evaporate at room temperature. Water (2 l) was added and the resulting mixture was extracted with ether (4 X 500 ml). The organic solution was washed with saturated aqueous sodium chloride and concentrated to a volume of about 100 ml. To this solution were added methanol (750 ml), water (80 ml), and concentrated hydrochloric acid (15 ml). The mixture was heated under reflux for 1 hr. under a nitrogen atmosphere. The resulting solution was concentrated to a volume of ca. 200 ml and then diluted with water (300 ml). Drying (magnesium sulfate) filtration and concentration gave the crude product which was distilled under reduced pressure to give 3,4-dimethyl-2-cyclohexen-1-one (27) (45.95 g; 66% yield): b.p. 30-36°C/0.8 Torr; ir ($CHCl_3$) 1675 and 1622 cm^{-1} (conjugated ketone); nmr ($CDCl_3$) δ 5.78 (s, 1H, $-\overset{|}{C}=CH-$), 1.94 (s, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 124.0891 (Calcd. for $C_8H_{12}O$: 124.0888).

7-Acetoxy-5,6-dimethylbicyclo[4.2.0]octan-2-one (28)

A solution of 3,4-dimethyl-2-cyclohexen-1-one (27) (20.45 g, 0.16 mol) and vinyl acetate (370 ml) in benzene (566 ml) was placed in a photochemical reaction apparatus (figure 2). A stream of dry nitrogen gas was maintained to agitate the solution. Crushed ice and water were placed in the outer dewar flask containing the reaction flask to cool the reaction mixture. Irradiation was carried out using a 450W Hanovia high-pressure quartz mercury-vapor lamp with a Pyrex filter for 20 hr. Concentration of the resulting solution gave a viscous oil which was distilled at reduced pressure to give a diastereomeric mixture of keto acetate 28 (26.13 g; 75% yield): b.p. 114-116°C/1.2 Torr; ir ($CHCl_3$) 1741 (ester) and 1706 cm^{-1} (ketone); nmr ($CDCl_3$) δ 5.50-4.70 (complex, 1H, $-\overset{|}{C}H-O-$), 2.07, 2.04 and 2.02 (s, total 3H, CH_3COO-); ms M^+ 210.1232 (Calcd. for $C_{12}H_{18}O_3$: 210.1260).

7-Hydroxy-5,6-dimethylbicyclo[4.2.0]octan-2-one (29)

To a solution of keto acetate 28 (26.13 g, 0.12 mol) in methanol (260 ml) and water (60 ml), a 2N aqueous solution of sodium hydroxide (200 ml) was added. The resulting brown solution was heated under reflux for 1 hr. After most of the methanol was removed under reduced pressure, water (250 ml) was added. The aqueous solution was extracted with ether (4 X 200 ml), washed with saturated aqueous sodium chloride (2

X 200 ml), dried (magnesium sulfate), filtered and concentrated. The crude product was distilled under reduced pressure to give a diastereomeric mixture of keto alcohols 29 (15.22 g; 76% yield): b.p. 120-130 °C/1.4 Torr; ir ($CHCl_3$) 3238 (alcohol) and 1684 cm^{-1} (ketone); nmr ($CDCl_3$) δ 4.30-3.90 (complex, 1H, $=C\underline{H}-OH$) and 1.28-0.86 (complex, 6H, methyls); ms M^+ 168.1150 (Calad. for $C_{10}H_{16}O_2$: 168.1148).

2,2-Ethyldithio-5,6-dimethylbicyclo[4.2.0]octan-7-ol (30)

Keto alcohol 29 (77 g,0.46 mol) was dissolved in 1,2-ethanedithiol (300 ml, 3.6 mol). The solution was chilled to 0 °C and boron trifluoride etherate (12.6 ml) was then added slowly. The mixture was stirred under a nitrogen atmosphere at room temerature for 20 hr. The reaction mixture was poured into an ice-cold 2N aqueous sodium hydroxide solution (400 ml), and extracted with chloroform (4 X 200 ml). Drying (magnesium sulfate), filtration and concentration gave the crude product which was pruified by column chromatography on silica gel. Elution with petroleum ether-ethyl acetate (10:1) gave one of the isomers 30a (9.14 g) which crystallized on standing: m.p. 88-90 °C; ir ($CHCl_3$) 3320 cm^{-1} (alcohol); nmr($CDCl_3$) δ 4.06 (t, 1H, J = 7 Hz, $-\overset{|}{C}\underline{H}-OH$), 3.30 (m, 5H, $-S-CH_2CH_2-S$ and $-OH$), 1.22 (s, 3H, $-\underset{|}{\overset{|}{C}}-CH_3$) and 1.12 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 244.0954

(Calcd. for $C_{12}H_{20}OS_2$: 244.0956).

Anal. Calcd. for $C_{12}H_{20}OS_2$: C, 58.99; H, 8.26; S, 26.20 Found: C, 59.12; H, 8.35; S, 26.55.

Further elution wth the same solvent system afforded a mixture of additional diastereomers of alcohol 30 (80 g): ir ($CHCl_3$) 3396 cm^{-1} (alcohol); nmr ($CDCl_3$) δ 4.32- 3.74 (complex, 1H, $-\overset{|}{C}\underline{H}-OH$), 3.29 (s, 5H, $-S-CH_2CH_2-S-$ and -OH) and 1.16-0.82 (complex, 6H, methyls); ms M^+ 244.0951 (Calcd. for $C_{12}H_{20}OS_2$: 244.0956). The total yield of alcohols 30 was 80%.

2,2-Ethylenedithio-5,6-dimethylbicyclo[4.2.0]octan-7-one (31a, 31b)

To a solution of alcohol 30a (2.33 g, 0.01 mol) in dimethylsulfoxide (28.7 ml), was added acetic anhydride (19 ml). The reaction mixture was kept at 5 °C for 24 hr. After that period, water (25 ml) was added and the resulting solution was stirred at room temperature for 1 hr. Ice-cold 2N aqueous sodium hydroxide (50 ml) was added. The mixture was extracted with dichloromethane (4 X 250 ml), dried (magnesium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate afforded ketone 31a (2.07 g; 90% yield): m.p. 73-74 °C; ir ($CHCl_3$) 1776 cm^{-1}

(four-membered ring ketone); nmr ($CDCl_3$) o 3.40 (m, 4H, $-S-CH_2CH_2-S-$), 1.28 (s, 3H, $-C-CH_3$) and 1.02 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 242.0789 (Calcd. for $C_{12}H_{18}OS_2$: 242.0799); cmr ($CDCl_3$) δ 213.6, 67.4, 66.4, 48.6, 47.0, 40.7, 38.0, 34.1, 33.0, 28.3, 21.8 and 16.6.

Anal. Calcd. for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.49; S, 26.65
Found: C, 59.61; H, 7.48: S, 26.95.

Similar reaction was carried out with the diastereomeric mixture of alcohol 30 (1 g, 4 mmol) and it gave a mixture of ketones 31a and 31b (0.6 g, 67% yield) in 1:2 ratio by nmr integration: m.p. 104-106 °C; ir ($CHCl_3$) 1780 and 1760 cm^{-1} (four-membered ring ketones); nmr ($CDCl_3$) δ 3.36 (s, 4H, $-S-CH_2CH_2-S-$), 1.28, 1.12 (both s, total 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.02 and 0.94 (both d, total 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 242.0793 (Calcd. for $C_{12}H_{18}OS_2$: 242.0799).

8-Carbethoxy-2,2-ethylenedithio-5,6-dimethylbicyclo-[4.3.0]nonan-7-one (32)

At 0 °C, to a solution of ketone 31a (2.32 g, 0.01 mol) in dry ether (70 ml), 24.92 mmol). After stirring for 5 min. under an atmosphere of nitrogen, ethyl diazoacetate (2.61 ml, 24.84 mmol) was added slowly through a syringe. The flask was then wrapped with aluminum foil to exclude light and the reaction mixture was allowed to warm up to room

temperature. After stirring for 23 hr, it was chilled to 0 °C and saturated aqueous sodium bicarbonate (50 ml) was added with care. The mixture was extracted with dichloromethane (4 X 100 ml), dried (magnesium sulfate), filtered and concentrated. The reddish oil thus obtained was further concentrated *in vacuo* for 24 hr. Column chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate, afforded keto ester **32** (1.59 g; 51% yield) which crystallized on standing: m.p. 79-81 °C; ir ($CHCl_3$) 1749 (five-membered ring ketone) and 1722 cm^{-1} (ester); nmr ($CDCl_3$) δ 4.22 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.32(s, 4H, $-S-CH_2CH_2-S-$), 1.32 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$), 1.30 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$) and 1.15 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 328.1167 (Calcd. for $C_{16}H_{24}O_3S_2$: 328.1167).

8-Carbethoxy-2,2-ethylenedithio-5,6-dimethylbicyclo[4.3.0]nonan-7-ol (34a, 34b)

Keto ester **32** (3.68 g, 0.01 mol) was dissolved in absolute ethanol (50 ml). The solution was then chilled to 0 °C and sodium borohydride (1.79 g, 0.04 mol) was added. The reaction mixture was stirred under an argon atmosphere at 0 °C for 7 hr. Water (5 ml), saturated aqueous ammonium chloride (5 ml) and 2N aqueous hydrochloric acid (10 ml) were sequentially added. The resulting solution was

extracted with dichloromethane (4 X 100 ml), dried (magnesium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate afforded two isomeric alcohols 34a and 34b. The minor (807 mg) and the faster-moving one 34a was obtained as a liquid: ir ($CHCl_3$) 3471 (alcohol) and 1732 cm^{-1} (ester); nmr ($CDCl_3$) δ 4.22 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 4.03 (s, 1H, -OH), 4.10 (d, 1H, J = 5 Hz, $-\overset{|}{C}\underline{H}-OH$), 3.30 (s, 4H, $S-CH_2CH_2-S-$), 1.30 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.15 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$) and 0.98 (s, 3H, $-\underset{|}{\overset{|}{C}}-CH_3$); ms M^+ 330.1321 (Calcd. for $C_{16}H_{26}O_3S_2$: 330.1323).

Anal. Calcd. for $C_{16}H_{26}O_3S_2$: C, 58.16; H, 7.94; S, 19.36 Found: C, 58.04; H, 7.74; S, 19.29.

The major isomer 34b (1.10 g) was obtained in crystalline form: m.p. 99-101 °C; ir ($CHCl_3$) 3505 (alcohol) and 1726 cm^{-1} (ester); mnr ($CDCl_3$) δ 4.20 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 4.16 (s, 1H, -OH), 4.12 (d, 1H, J = 5 Hz, $-\overset{|}{C}\underline{H}-OH$), 3.32 (s, 4H, $-S-CH_2CH_2-S-$), 1.29 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.22 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$) and 1.10 (s, 3H, $-\underset{|}{\overset{|}{C}}-CH_3$); ms M^+ 330.1319 (Calcd. for $C_{16}H_{26}O_3S_2$: 330.1323).

Anal. Calcd. for $C_{16}H_{26}O_3S_2$: C, 58.16; H, 7.94; S,19.36 Found: C, 57.88; H, 7.81; S, 19.27.

8-Carbethoxy-5,5-ethylenedithio-9-mesyl-1,2-dimethylbicyclo[4.3.0]nonane (35a, 35b)

To a solution of alcohol 34a (55 mg, 0.17 mmol) in dry pyridine (1 ml), were added a catalytic amount of 4-N,N-dimethylaminopyridine and methanesulfonyl chloride (0.04 ml, 0.51 mmol). After stirring at room temperature for 24 hr, the reaction mixture was diluted with dichloromethane (2 ml), washed with aqueous ammonium hydroxide and aqueous hydrochloric acid, dried (magnesium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate, afforded mesylate 35a (50 mg, 81% yield): ir ($CHCl_3$) 1734 cm^{-1} (ester); nmr ($CHCl_3$) δ 5.16 (d, 1H, J = 4 Hz, $-\overset{|}{C}\underline{H}-OSO_2CH_3$), 4.20 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.29 (s, 4H, $-S-CH_2CH_2-S-$), 3.08 (s, 3H, $-OSO_2CH_3$), 1.31 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.17 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$) and 1.15 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 408.1105 (Calcd. for $C_{20}H_{24}O_5S_2$: 408.1065).

Similar reaction was carried out for alcohol 34b (54 mg, 0.17 mmol), and mesylate 35b was obtained in quantitative yield: ir ($CHCl_3$) 1730 cm^{-1} (ester); nmr ($CDCl_3$) δ 5.07 (d, 1H, J = 4 Hz, $-\overset{|}{C}\underline{H}-OSO_2CH_3$), 4.21 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.29 (s, 4H, $-S-CH_2CH_2-S-$), 3.10 (s, 3H, $-OSO_2CH_3$), 1.30 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.20 (d, 3H, J = 6 Hz, $-C\underline{H}_3$) and 1.15 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$); ms M^+ 408.1094 (Calcd. for $C_{17}H_{28}O_5S_3$: 408.1099).

9-Acetoxy-8-carbethoxy-5,5-ethylenedithio-1,2-dimethylbicyclo[4.3.0]nonane (37)

Alcohol 35b (110 mg, 0.34 mmol) was dissoloved in dry pyridine (4 ml). Acetic anhydride (1 ml) was added. The reaction was allowed to proceed at room temperature for 24 hr. Upon completion of the reaction, the mixture was concentrated *in vacuo*. After column chromatography of the residue on silica gel with petroleum ether-ethyl acetate elution, acetate 37 (123 mg; 99% yield) was obtained and showed the following spectral data: ir ($CHCl_3$) 1736 cm^{-1} (ester); nmr ($CDCl_3$) δ 5.06 (d, 1H, J = 4 Hz $-\overset{|}{C}\underline{H}OOCH_3$), 4.18 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.28 (s, 4H, $-S-CH_2CH_2-S-$), 2.10 (s, 3H, CH_3COO-), 1.27 (t, 3H, J = 6 Hz, $-COOCH_2C\underline{H}_3$), 1.15 (s, 3H, $-\underset{|}{\overset{|}{C}}-CH_3$) and 1.05 (d, 3H, J = 7 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 372.1427 (Calcd. for $C_{18}H_{28}O_4S_2$: 372.1429).

Anal. Calcd. for $C_{18}H_{28}O_4S_2$: C, 58.04; H, 7.58; S, 17.18

Found: C, 58.26, H, 7.66; S, 16.93.

8-Carbethoxy-6,5-ethylenedithio-1,2-dimethylbicyclo-[4.3.0]non-8-ene (36)

Mesylate 35a (121 mg, 0.30 mmol) was dissolved in freshly distilled 1,2-dimethoxyethane (3 ml). The solution was then chilled to 0 °C and sodium hydride (50% dispersion in oil; 25 mg, 0.5 mmol) was added. After stirring at room

temperature under an argon atmosphere for 1 hr, aqueous ammonium chloride (3 ml) was added. The mixture was extracted with dichloromethane (4 X 10 ml), dried (magnesium sulfate), filtered and concentrated. Column chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate, afforded unsaturated ester 36 (74 mg; 80% yield). Under the same conditions, mesylate 35b (66 mg, 0.16 mmol) and acetate 37 (92 mg, 0.25 mmol) gave the same ester 36 in 86% (43 mg) and 99% (76 mg) yields respectively. The following spectral data were obtained for 37: ir ($CHCl_3$) 1714 (ester) and 1614 cm^{-1} (olefin); nmr ($CDCl_3$) δ 6.57 (s, 1H, $-C\underline{H}=C-COOCH_2CH_3$), 4.22 (q, 2H, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 3.25 (m, 4H, $-S-CH_2CH_2-S-$), 1.32 (t, 3H, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.23 (s, 3H, $-\overset{|}{\underset{|}{C}}-CH_3$) and 0.98 (d, 3H, J = 6 Hz, $-\overset{|}{C}H-C\underline{H}_3$); ms M^+ 312.1221 (Calcd. for $C_{16}H_{24}O_2S_2$: 312.1218).

8-Carbethoxy-1,2-dimethylbicyclo[4.3.0]non-4,8-diene (38)

To a solution of (36) (589 mg, 1.89 mmol) in dry bezene (30 ml) freshly prepared Raney Nickel (W-2, 6 ml) was added. The solution was stirred at room temperature under an argon atmosphere for 5 days. The mixture was then filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate afforded diene ester 38 (300 mg, 72% yield): ir ($CHCl_3$) 1715 (ester)

and 1630 cm^{-1} (olefins); nmr (CDCl$_3$) δ 6.74 (m, 1H, $\text{-C}\underline{\text{H}}\text{=C-COOCH}_2\text{CH}_3$), 5.55 (m, 2H, -HC=CH-), 4.18 (q, 2H, J = 7 Hz, $\text{-COOC}\underline{\text{H}}_2\text{CH}_3$), 1.39 (t, 3H, J = 7 Hz, $\text{-COOCH}_2\text{C}\underline{\text{H}}_3$), 1.10 (s, 3H, $\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-CH}_3$) and 1.04 (d, 3H, J = 6 Hz, $\text{-}\overset{|}{\text{C}}\text{H-C}\underline{\text{H}}_3$); ms M$^+$ 220.1461 (Calcd. for $C_{14}H_{20}O_2$: 220.1463).

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.31; H, 9.16

Found: C, 76.08; H, 9.56.

8-Carbethoxy-1,2-dimethylbicyclo[4.3.0]nonane (23a, 23b)

To a solution of diene ester 38 (126 mg, 0.57 mmol) in absolute ethanol (5 ml), freshly prepared Raney Nickel (W-2; 4 ml) was added. It was then stirred under an atmosphere of hydrogen at room temperature for 24 hr. The reaction mixture was filtered and concentrated. Flash chromatography of the residue on silica gel, eluting with petroleum ether-ethyl acetate, gave a mixture of two epimeric esters 23a, and 23b (125 mg; 97% yield) in ca. 2:3 ratio as indicated by the nmr spectrum (CDCl$_3$) which showed a major set of signals at δ 4.16 (q, 2H, J = 7 Hz, $\text{-COOC}\underline{\text{H}}_2\text{CH}_3$), 2.94 (m, 1H, $\text{-CH}_2\text{-}\overset{|}{\text{C}}\underline{\text{H}}\text{-CH}_2\text{-}$), 1.28 (t, 3H, J = 7 Hz, $\text{-COOCH}_2\text{C }\underline{\text{H}}_3$). 0.98 (s, 3H, $\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-CH}_3$) and 0.88 (d, 3H, J = 6 Hz, $\text{-}\overset{|}{\text{C}}\underline{\text{H}}\text{-CH}_3$) and a minor set of signals at δ 4.16 (q, 2H, J = 7 Hz, $\text{-COOC}\underline{\text{H}}_2\text{CH}_3$), 2.94 (m, 1H, $\text{-CH}_2\text{-}\overset{|}{\text{C}}\underline{\text{H}}\text{-CH}_2\text{-}$), 1.28 (t, 3H, J = 7 Hz, $\text{-COOCH}_2\text{C}\underline{\text{H}}_3$), 1.01 (s, 3H, $\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-CH}_3$) and o.88 (d, 3H, J = 6 Hz, $\text{-}\overset{|}{\text{C}}\text{H-C}\underline{\text{H}}_3$); ir

($CHCl_3$) 1734 cm^{-1} (ester); ms M^+ 224.1774 (Calcd. for $C_{14}H_{24}O_2$: 224.1776).

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.94; H, 10.79; O,14.27
Found: C, 73.75; H, 10.59; O,14.03.

REFERENCES

1. K. Naya. I, Takagi, M. Hayashi, S. Nakamura, M. Kobayashi and S. Katsumura, Chem. Ind. (London), 318, (1968).
2. K. Naya, M. Hayashi, I. Takagi, S Nakamura and M. Kobayashi, Bull. Chem. Soc. Japan, 45, 3673 (1972).
3. K. Naya and M. Kobayashi, Bull. Chem. Soc. Japan, 44, 258 (1971).
4. K. Shirahata, T. Kato, M. C. Woods and Y. Kitahara, Tetrahedron Lett., 369 (1968).
5. N. Abe, T. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, K. Ro and T. Kurihara, Tetrahedron Lett., 1993 (1968).
6. K. Shirahata, N. Abe, T. Kato and Y. Kitahara, Bull. Chem. Soc. Japan, 41, 1732 (1968).
7. K. Shirahata, T. Kata and Y. Kitahara, Tetrahedron, 25, 3179 (1969).
8. H. Shibata and S. Shimizu, Agric. Biol. Chem., 42, 1427 (1978).
9. H. Shibata and S. Shimizu, Koen Yoshishu - Koryo Terupen oyolii Seiyu Kagaku ni kansura Torenkai 23rd, 200 (1979).
10. K. Ito, T. Iida, C. Takeichi and Yakugaku Zasshi, 98,

1592 (1978).

11. F. Bohlmann, C. Zdero, D. Berger, A. Suwita, P. Mahanta and C. Jeffrey, Phytochemistry, 18, 79 (1979).
12. K. Naya, I. Takagi, Y. Kawaguchi and Y. Asada, Tetrahedron, 24, 5871 (1968).
13. J. A. Marshall and G. M. Cohen, J. Org. Chem., 36, 877 (1971).
14. L. Novonty, B. Herout and F. Sorm, Tetrahedron Lett., 697 (1961).
15. V. Herout, "Aspects of Terpenoid Chemistry and Biochemistry," ed. by T. W. Goodwin, Academic Press, Inc., London and New York, 1971, Chap. 3.
16. G. W. K. Cavill and C. D. Hall, Tetrahedron, 23, 1119 (1967).
17. W. Reusch and P. Mattison, Tetrahedron, 23, 1953 (1967).
18. S. A. A. Achmad and G. W. K. Cavill, Aust. J. Chem., 16, 858 (1963).
19. D. A. Evans and C. L. Sims, Tetrahedron Lett., 4691 (1973).
20. D. A. Evans and G. Andrews, Tetrahedron Lett., 5121 (1972).
21. K. Hayashi, H. Nakamura and H. Mitsuhashi, Chem. Pharm. Bull., 21, 2806 (1973).

22. H. J. Liu and T. Ogino, Tetrahedron Lett., 4937 (1973).

23. A. J. Birch, J. Chem. Soc., 430 (1944).

24. P. E. Eaton, Acc. Chem. Res., 1, 50 (1968).

25. E. J. Corey, R. B. Mitra and H Vela, J. Amer. Chem. Soc., 86, 485 (1964).

26. E. J. Corey and S. Nozae, J. Amer. Chem. Soc., 86, 1652 (1964).

27. E. J. Corey, J. D. Bass, R. LeMahieu and R. B. Mitra, J. Amer. Chem. Soc., 86, 5570 (1964).

28. P. J. Barry and B. M. Craig, Can. J. Chem., 33, 716 (1955).

29. N. Pappas and H. R. Nace, J. Amer. Chem. Soc., 81, 4556 (1959).

30. J. D. Albright and L. Goldman, J. Amer. Chem. Soc., 87, 4214 (1965).

31. W. T. Tai and E. W. Warnhoff, Can. J. Chem., 42, 1333 (1964).

32. H. J. Liu and S. P. Majumder, Syn. Comm., 5, 125 (1975).

33. O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, J. Amer. Chem. Soc., 75, 1286 (1953).

34. G. R. Pettit and E. E. van Tamelen, Org. React., 12, 356 (1962).

35. H. Hamptmann and W. F. Walter, Chem. Rev., 62, 347 (1962).

36. R. Mozingo, Org. Syn., Coll. Vol., 3, 181 (1955).

37. G. Zweifel and H. C. Brown, Org. React., 13, 28 (1963).

38. W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).

B30354